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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EPPS, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,127	PANCHAL ET AL.	
	Examiner	Art Unit	
	Janet L Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 January 1939* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 32 and 37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The method of use referred to in these claims implies *in vivo* applicability for enablement purposes. The applicant has only provided *in vitro* data (using Xeroderma Pigmentosum group A cells) demonstrating the ability of a human arginine opal suppressor tRNA to partially restore the activity of the nonsense mutated XPAC gene. There are no working *in vivo* examples provided demonstrating the efficacy of this treatment on humans with Xeroderma Pigmentosa.

One reference cited in the specification, Li et al., have demonstrated that local injection of a tRNA suppressor gene, naked plasmid DNA, into the mdx rat (animal model for Duchenne muscular dystrophy) can rescue gene expression lost due to an ochre mutation. However, Li et al. cite that applying this type of system to other organisms largely depends upon the successful development of vectors that can deliver the therapeutic suppressor tRNA gene more efficiently to allow for a sustainable gene expression. In addition, Li et al cite that one major concern for the use of tRNA suppressors in human gene therapy is their potential toxic effects. More specifically, whether the introduction of a tRNA suppressor may potentially cause a read through

in other genes, subsequently leading to changes in the functions of their gene products. This observation of Li et al. suggests that the effects of a tRNA suppressor in a cell, as it relates to non-specific gene regulation, are unpredictable. Furthermore, potential effects produced by administration of a tRNA molecule to a cell may be associated with non-specific regulation of non-targeted genes, thereby making interpretation of experimental results problematic.

In addition, **In re Wands**, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988) lists eight considerations in determining whether or not undue experimentation would be involved in practicing inventions. These factors are: the quantity of experimentation necessary, the amount of direction or guidance needed, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, predictability or unpredictability of the art and the breadth of the claims. The amount of experimentation necessary to determine the appropriate mode of delivery of the suppressor tRNA gene sequence into an animal, to access the possible toxicological effects the treatment may have on the translation of other known and unknown proteins in each cell in said animal is beyond the scope of one with ordinary skill in the art. The instant application contains no guidance in performing all of these experiments, which adds to the difficulty in practicing the invention. The examples presented in the specification do not adequately describe how to use the present invention embodied by claims 32 and 37. When the Wands factors are weighed, it is concluded that undue experimentation would be required to practice the invention throughout the full scope of the claims, and therefore the invention is not enabled.

3. Claim 19 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the pHhargsuptRNAOpal vector is required to practice the claimed invention. As a required element, this vector must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 U.S.C. 112, first paragraph, may be satisfied by a deposit of the pHhargsuptRNAOpal vector; see 37 C.F.R. 1.802. The specification does not provide a repeatable method for obtaining the pHhargsuptRNAOpal vector and it does not appear to be a readily available material. Deposit of the pHhargsuptRNAOpal vector would satisfy the enablement requirements of 35 U.S.C. 112.

It does not appear that such a deposit of the pHhargsuptRNAOpal vector has been made; therefore the necessary criteria of the deposit rules under the terms of the Budapest Treaty have not been met. See the attached suggestion for the deposit of biological materials. Submission of an amendment to the specification or a declaration showing a deposit of the pHhargsuptRNA^{Opal} vector as suggested will satisfy the deposit requirements. See 37 CFR 1.801-37 CFR 1.809.

4. Claims 7, 12, and 26 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7, 12, and 26 recite an oligonucleotide that has a sequence selected from the group consisting of SEQ ID NO: 1-10, their complements, and their functional equivalents.

However, the specification as filed does not provide an adequate description of the full scope of compounds that are "functional equivalents," of the oligonucleotides according SEQ ID NO: 1-10. The specification as filed, page 6, last paragraph, states that "the term 'functional equivalent,' includes derivatives in which nucleotide base(s) and/or amino acids have been added, deleted or replaced without a significant adverse effect on biological function and which hybridizes under high conditions of stringency. " However, applicants have not provided sufficient guidance that would allow one of skill in the art to predict the structure of oligonucleotides comprising additions, deletions or substitutions and still maintain the ability to function in the same manner as SEQ ID NO: 1-10. Moreover, it is unclear what function applicants are referring to. Apart from trial and error experimentation, one of skill in the art would not be able to describe full scope of compounds encompassed by the claimed invention.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical

formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

In view of the need for further experimentation in order to isolate the full scope of compounds encompassed by the claimed invention, it is evident that the full scope of the claimed invention was not ready for patenting at the time of filing.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 10-12, 23-26, 33-36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 10-12 recite "[T]he oligonucleotide of claim 8," however claim 8 is drawn to a method. Claims 10-12 are vague and indefinite since it is unclear if these claims are drawn specifically to an oligonucleotide or to a method.

Claims 23-26 recite "[T]he oligonucleotide of claim 22," however claim 22 is drawn to a method. Claims 23-26 are vague and indefinite since it is unclear if these claims are drawn specifically to an oligonucleotide or to a method.

Claims 33-36 recite "the oligonucleotide of claim 32," there is lack of antecedent basis for the limitation "the oligonucleotide" in claim 32. Claim 32 is drawn to a method and not to an oligonucleotide.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-6, 8-11, 13-15, 16-22, and 24-25, and 38-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharp et al., Temple et al., Li et al., Noren et al. and Atkinson et al.

Sharp et al. disclose a method of designing tRNAs which suppress nonsense codons in a gene in a mammalian cell, said method comprising 1) preparing an oligonucleotide primer comprising a region complementary to the nonsense codon; 2) preparing a DNA template for production of a tRNA molecule; 3) forming a suppressor gene from said template and primer by site specific mutagenesis; and 4) transforming the suppressor gene into a mammalian cell, whereby the nonsense codon will be suppressed. This method also includes preparing a template for the insertion of an amino acid chosen from the group consisting of: tyrosine, serine, lysine, tryptophan, leucine, glutamine, glutamic acid, and glycine. Included within the embodiments of this invention are SV40 plasmid vectors containing the suppressor tRNA genes (US Patent No. 4,687, 737; column 2). In addition, Sharp et al. teach a method of monitoring the transduction of cells comprising introducing a suppressor tRNA into cells containing a nonsense mutation in a reporter gene, and observing the expression of the reporter gene as a result of the suppressor tRNA restoring translation of the reporter gene product (col. 7-8).

Temple et al. disclose a functional human suppressor lysine tRNA (containing an anticodon which recognizes the amber termination codon UAG) gene whose length is

approximately 76 base pairs, this gene was subcloned into M13mp7 phage. This suppressor lysine tRNA was able to suppress the amber nonsense mutation in β-thalassaemia (p. 338). Li et al. teach the use of a human suppressor serine tRNA which has functions in the rescue of mdx (gene associated with Muscular Dystrophy in humans) gene expression lost due to an Ochre (UAA) mutation.

Noren et al. teach a method of site specific incorporation of un-natural amino acids into proteins, wherein said method comprises replacement of a codon encoding an amino acid of interest, replacing the codon with a nonsense codon (TAG) by oligonucleotide directed mutagenesis, and designing a suppressor tRNA chemically aminoacylated in vitro to recognize the nonsense codon and direct the amino acid into the protein at the target site (p. 182-183). Both natural and un-natural amino acids can be incorporated into a protein by this method.

Atkinson et al. teach that since the promoters for eukaryotic tRNA genes lie within the structural sequences encoding the tRNA molecule itself, the length of the active transcriptional unit of a tRNA gene may be considerably less than 500 base pairs so that accommodation into a delivery vector may be facilitated (page 1327). In addition, based upon an analysis of codons altered by nonsense mutations, Atkinson et al. suggest that UAG suppressor tRNAs should be designed charged with Trp, Gln and Glu, UAA suppressor tRNAs should be designed charged with Gln and Glu and UGA suppressor tRNAs should be designed charged with Arg (page 1332).

Although these references do not teach two oligonucleotides in tandem both encoding suppressor tRNA genes, these references do teach oligonucleotides that encode suppressor tRNA genes, the added limitation in claim 4 is an obvious modification of claim 1. In view of the

general method of designing and using suppressor tRNAs to by-pass nonsense mutations in proteins in mammalian cells as taught by Sharp et al., the ability of human suppressor tRNAs to suppress nonsense mutations in genes associated with diseases in humans as taught by Tempel et al. and Li et al., the study of codons altered by nonsense mutations and the knowledge given relating to the structure of the tRNA molecule regarding the positioning of regulatory elements taught by Atkinson et al. , it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing of the instant application to design oligonucleotides encoding human suppressor tRNAs of less than 500bp and to design methods of use of said human suppressor tRNAs embraced by the claimed invention.

Addtionally, Applicant's oligonucleotides which encode a synthetic suppressor tRNA and those disclosed in the above references have similar properties, and it is deemed that since such is the case, other claimed limitations not disclosed are deemed obvious. Sufficient evidence of similarity is present to shift the burden to Applicant to provide evidence that the claimed products are unobviously different than the suppressor tRNA molecules disclosed in the references described above. **In re Best**, 195 USPQ 430 (CCPA 1977).

9. Claims 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sharp et al., Temple et al., Li et al., Noren et al. and Atkinson et al. as applied above and further in view of Okasinski.

Sharp et al., Temple et al., Li et al., Noren et al. and Atkinson et al. teach a general method of designing and using suppressor tRNAs to by-pass nonsense mutations in proteins in mammalian cells (Sharp et al.), the ability of human suppressor tRNAs to suppress nonsense mutations in genes associated with diseases in humans (Tempel et al. and Li et al.), and the study

of codons altered by nonsense mutations and the knowledge given relating to the structure of the tRNA molecule regarding the positioning of regulatory elements (Atkinson et al.).

None of the above references teach the use of an HSV vector comprising a nucleotide encoding a human suppressor tRNA molecule according to claim 1 of the instant application.

Okasinski teaches that the HSV (Herpes-simplex virus) vector can be used to produce a helper free viral vector. The invention disclosed by Okasinski an eukaryotic expression vector containing HSV DNA and regulatory elements, and sites for subcloning a DNA of interest. In addition, Okasinski discloses methods of producing a mammalian cell line having cells containing the expression vector.

Therefore, in view of the teachings of the general method of designing and using suppressor tRNAs to by-pass nonsense mutations in proteins in mammalian cells as taught by Sharp et al., the ability of human suppressor tRNAs to suppress nonsense mutations in genes associated with diseases in humans as taught by Tempel et al. and Li et al., the study of codons altered by nonsense mutations and the knowledge given relating to the structure of the tRNA molecule regarding the positioning of regulatory elements taught by Atkinson et al, and finally the advantages associated with the use of HSV vectors taught by Okasinski, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing of the instant application to design oligonucleotides encoding human suppressor tRNA molecules subcloned into HSV vectors in order to produce a cell line expressing said human suppressor tRNA molecules.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-27, 29-31 and 38-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of U.S. Patent No. 6,309,830. Although the conflicting claims are not identical, they are not patentably distinct from each other because the issued claims are an obvious variation of the claims recited in the instant application. The issued claims differ from the pending claims, for example, issued claim 1 is limited to a synthetic suppressor tRNA consisting of elements (A-C), and pending claim 1 are drawn to synthetic suppressor tRNA molecules comprising elements (A-C). The pending claims encompass synthetic suppressor tRNA molecules comprising a sequence that is of a length greater than 150 nucleotides, and those of the issued claims are limited to 150 nucleotides in length. Moreover, it would have been obvious to modify the claims of the pending application

to recite wherein the oligonucleotides consist of 150 nucleotides since the specification as filed, see page 13, 3rd paragraph, recite that oligonucleotides that are small, around 100 nucleotides long are easier to handle than longer sequences comprising the full length tRNA sequence. Therefore, the claims of the issued US patent represent an obvious variation of the claims of the pending application.

11. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

12. Claim 28 is rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 24 of prior U.S. Patent No. 6,309,830. This is a double patenting rejection.

Cited References

13. Other than US Patent 6,309,830 B1 all references were previously forwarded to Applicants during the prosecution of parent application 09/229,212.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 703-308-8883. The examiner can normally be reached on M-T, Thurs-Friday 9:00AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703)-308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-746-5143 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE
March 6, 2003

SEAN McGARRY
PRIMARY EXAMINER
1635